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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	15

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,546	CLARK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-4,6-16 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,6-16 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 14 on 7/31/03.

Claims 5 and 17-28 were canceled and claim 29 was added as requested.

Claims 1-4, 6-16 and 29 are pending and under consideration in this Office Action.

Specification

Applicant's amendment was sufficient to overcome the objection to the disclosure due to an embedded hyperlink and/or other form of browser-executable code.

Claim Objections

Applicant's amendment was sufficient to overcome the objection to the claims 11-16 over the acronym "PCR".

Compliance with Sequence Rules

Applicant's amendment was sufficient to place the Application in compliance with 37 C.F.R.1.821-1.825.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 6-16, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using SEQ ID NO:4 or its

complement, or fragments thereof, to detect or amplify nucleic acids encoding the polypeptide of SEQ ID NO:5, does not reasonably provide enablement for methods of detecting or amplifying nucleic acids encoding a "Rig" polypeptide other than SEQ ID NO:5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 6-10 are drawn to methods of detecting nucleic acids encoding "Rig" in a sample by detecting a hybridization complex between a probe having complementarity to at least a portion of SEQ ID NO:4 and a nucleic acid. Claims 11-16 and 29 are drawn to methods of amplifying by PCR a nucleic acid encoding Rig. The specification teaches that, in one embodiment, Rig is encoded by SEQ ID NO:4 and has the amino acid sequence of SEQ ID NO:5 (see page 5, lines 5-8).

The scope of the claimed invention is unclear because the specification fails to give an adequate definition of what is, and is not, a Rig polypeptide. The specification provides guidance as to the function of the version of Rig that is SEQ ID NO:5. This protein is expressed in fetal and adult brain and heart, but not in a variety of other tissues. Expression is reduced or zero in some tumor derived neuronal cell lines and tumor-derived tissue samples, but appears normal in others (see e.g. Fig. 12, lanes 3, 4, 6, and 9-12). Constitutive expression of SEQ ID NO:4 inhibits focus formation in NIH 3T3 cells. The protein antagonizes Ras-dependent Elk-1 transcription factor activity, and inhibits the growth of U251 and A673 neuronal tumor-derived cells when expressed ectopically in these lines. An S21N mutation of SEQ ID NO:5 (analogous to Ras S17N) causes transformation when expressed in NIH 3T3 cells. Finally, Rig coprecipitates with Raf-1, a kinase which is regulated by H-Ras and K-Ras. However, the specification fails to teach what are the minimum sequence and functional

characteristics a given polypeptide must have in order to be recognized as a Rig polypeptide. For example, the specification teaches that Noey2 is a related polypeptide (63% identity, see page 44, lines 24-29) that is similar to Rig inasmuch as it is a G-protein and appears to be a tumor suppressor, but it is unclear if Noey2 falls within the genus of Rig polypeptides. An alignment between the Noey2 polynucleotide sequence and SEQ ID NO:4 shows that there is a segment of 81% identity from position 307-364 of SEQ ID NO:4 (see attached alignment). So, while it is clear that this fragment of SEQ ID NO:4 could be used to identify Noey2 by hybridization, it is unclear if Noey2 falls within the claimed genus because the specification fails to adequately define what is a Rig polypeptide.

Even if the specification did define what functional attributes are required to qualify a polypeptide as a Rig polypeptide, it would fail to adequately enable the invention because neither it nor the prior art teaches the required structural limitations for Rig polypeptides, and one of skill in the art could not determine these without undue experimentation.

At the time the invention was filed the Ras protein superfamily contained about 150 members which functioned to transduce a wide variety of signals in cells. See Paduck et al (Acta Biochemica Polonica 48(4): 829-850, 2001) page 830, column 1, first line of last paragraph. These proteins all comprise a guanine nucleotide binding domain with a high affinity for GTP or GDP, and low (but extremely variable within the superfamily) catalytic activity. The nucleotide binding site also contributes to the binding of effector molecules which are activated by Ras and which mediate the wide variety of cellular responses. The phosphorylation state of the nucleotide in the binding site regulates the activity of the Ras protein, (GDP activates Ras, and GTP inactivates Ras), and influences recognition and binding of effector molecules. So, structural differences

between Ras molecules govern the rate at which GTP is hydrolyzed as well as the identity of effector molecules with which they interact, and consequently the nature of signals that are transduced. See page 833, column 1, last full paragraph of Paduck. Although various Ras nucleotide binding sites are well known and highly conserved, it is unclear what governs the substantial kinetic differences in GTP/GDP exchange observed in the various Ras proteins. See last sentence of paragraph bridging columns 1 and 2 on page 833 of Paduck.

Generally speaking, the effects of amino acid substitutions on polypeptide activity are unpredictable. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. These regions can tolerate only relatively conservative substitutions, or no substitutions. See Bowie et al (1990). The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence

alone. Decades of research have failed to produce such an algorithm". In the specific case of Ras proteins, Paduck teaches that the effects on the activity of the protein of mutations in the nucleotide binding site are unpredictable. Furthermore, site directed mutagenesis studies have shown that mutations affecting nucleotide binding, and therefore signal transduction, are not limited only to the nucleotide binding site, but are found in segments well outside the nucleotide binding site. See paragraph bridging columns 1 and 2 on page 834. Because neither the prior art nor the specification provides adequate guidance as to how to generally predict the effects of amino acid substitutions within even the highly conserved nucleotide binding site of Ras proteins, and because the specification fails to teach what are the structural limitations that define Rig polypeptides, one of skill in the art could not determine without undue experimentation what sequences other than SEQ ID NO:5 are Rig polypeptides, and could not practice methods of identifying or amplifying nucleic acids encoding Rig polypeptides other than SEQ ID NO:5. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will adequately maintain Rig structure and function. In the absence of such guidance, one of skill in the art would

have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

In summary, because the specification fails to adequately teach what is encompassed by the term "Rig", and fails to teach what are the structural and functional limitations of Rig polypeptides, one of skill in the art could not identify or amplify a nucleic acid encoding a Rig polypeptide, other than SEQ ID NO:5, without undue experimentation.

Written Description

Claims 6-16 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6-10 are drawn to methods of identifying species of the genus of polynucleotides encoding a Rig polypeptide. The species must be capable of hybridization with a probe having complementarity to at least a portion of SEQ ID NO:4. Claims 11-16 and 29 are drawn to methods of amplifying and identifying species of the genus of polynucleotides encoding a Rig polypeptide. The polynucleotides must have complementarity to at least a portion of SEQ ID NO:4.

As noted above under enablement, the scope of the claimed genuses is unclear because the specification fails to give an adequate definition of what is, and is not, a Rig polypeptide. The specification discloses the sequences of 8 Ras-related polypeptides, in addition to the sequence of Rig, but it is not clear whether or not these polypeptides are intended to be within the scope of the invention, because the specification fails to teach what are the minimum sequence and functional characteristics a given

polypeptide must have in order to be recognized as a Rig polypeptide. Furthermore, the claims recite no functional requirements and only limited structural requirements. Claim 16 is the narrowest claim because it requires that the primers used for amplifying genes must comprise SEQ ID NOS: 2 and 3, which are designed to amplify double stranded polynucleotides comprising SEQ ID NO:4. However, claims 6-16 require only partial complementarity of the recited probes or primers to SEQ ID NO:4. So, these claims embrace probes and primers that have large regions of non-complementarity to SEQ ID NO:4, and that can detect or amplify sequences that have little or no relationship to SEQ ID NO:4. Because the claims recite no functional limitations regarding the activity of the encoded polypeptide, the scope of the claimed genus is unclear and one of skill in the art could not conclude that Applicant was or was not in possession of the claimed genus at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 6-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-16 are indefinite because it is unclear what is intended by "Rig". The specification fails to give this term a limiting definition, and one of skill in the art cannot know the metes and bounds of the claims. For example it is unclear what are the minimum sequence and function characteristics a given polypeptide or polynucleotide must have in order to be defined as a "Rig" polypeptide or polynucleotide.

Claim 3 is indefinite because it is not a complete sentence. Claim 3 lacks a verb.

R sponse to Argum nts

Applicant's arguments filed 7/31/03 have been fully considered but they are not persuasive.

Applicant responds to the 35 USC 112 rejections at pages 8-10 of the response.

Indefiniteness

At page 8, Applicant argues, essentially, that because Applicant gives a single example of a Rig polypeptide, that one of skill in the art would know what is and is not a Rig protein. This argument is unpersuasive because Applicant has failed to point to any limiting definition of the term Rig that would distinguish Rig from any other Ras-related inhibitor gene. Applicant lists several characteristics of Rig proteins, such as membership in the Ras protein family, activity as an inhibitor of growth in tumor cell lines, particular expression patterns in tissues and tumors, focus formation inhibiting activity, and ability to bind Raf-1. However, the specification does not require that all of these characteristics are required of all Rig proteins, and fails to teach how many of these characteristics are required of any Rig protein. As discussed in the rejection, the specification fails to provide any minimum sequence and functional characteristics that can serve as a standard for determining what is a Rig protein, so one of skill in the art cannot know what are the metes and bounds of the protection that Applicant desires.

Written Description

Applicant argues at page 9 of the response that several functional characteristics of Rig are disclosed, and asserts that one of skill in the art would recognize as Rig proteins "those amino acid sequences having high identity with SEQ ID NO:5, wherein

the encoded protein functions according to a Rig protein." This argument is unpersuasive because Applicant as failed to define high identity "high identity", and because the specification fails to make a sufficient correlation between any structure and any function of a Rig polypeptide that would set the genus of Rig polypeptides apart from genuses of other Ras family members. As discussed under enablement, the Ras protein superfamily contains many members with similar structural domains such as nucleotide binding and effector domains, and differences in these structural domains account for differences in function amongst the members of the family. Adequate written description of a genus requires that one must describe a representative number of species by complete structure or by relevant identifying characteristics such as a correlation between structure and function. It follows that if one is to adequately describe the entire genus of Rig polypeptides, having described only a single species by complete structure, then one must provide a correlation between the structural and functional features that define the genus, i.e. those features that distinguish Rig from other Ras family members. In this case, as noted under indefiniteness rejections, the specification does not even set forth what are the minimal functional requirements that must be met in order to qualify as a Rig polypeptide, and even if it had done such, the specification still fails to describe what level of structural variability is allowed while still retaining the functional characteristics that define the genus. Applicant argues that one of ordinary skill in the art could distinguish Rig from other Ras family members and offers Figures 2 and 3 as evidence. Fig. 2 is simply an alignment of several Ras family members and does not provide any interpretation of the data that would support

Applicant's position. Fig. 3 is a dendrogram depicting evolutionary relationships among Ras family members as a function of sequence divergence. This Figure does not support Applicant's argument because it presents no data concerning the relationship between structure and function, and therefore provides no evidence that ay of Ras proteins in the Figure would not be considered a Rig protein, particularly Noey2 which has in common with Rig 63% amino acid sequence identity and tumor suppressor function.

Because the scope of the claimed genus is unclear due to a failure to define the required functional characteristics of the species, because only a single species of the claimed genus of Rig polypeptides is disclosed, and because no other species of the claimed genus has been described by relevant identifying characteristics, one of skill in the art could not conclude that Applicant was in possession of the genus of Rig polypeptides at the time of filing. Further, Applicant could not have been in possession of methods to detect or amplify nucleic acids from "a sample comprising a nucleic acid encoding Rig" because this genus of samples had not been adequately described.

It is further noted that for claims 6-10, the nucleic acid probe must have complementarity to only "a portion of" SEQ ID NO:4. This limitation broadly reads on probes having only a single base in common with SEQ ID NO:4. Because SEQ ID NO:4 contains all four bases, these claims place no structural limitations whatsoever on the nature of the nucleic acid probe used in the method. Claims 11-15, require oligonucleotide primers that are "complementary" to SEQ ID NO:4. The specification at paragraph 52 indicates that complementary nucleic acids may have as little as 31%

identity, and thus need not encode a single amino acid that is encoded by the region to which they are "complementary". These claims also fail to set forth any clear functional requirements of the Rig protein encoded in the sample, or of the Rig protein to be identified or amplified, so there can be no adequate written description of either one in view of the specification's disclosure of only a single species of Rig, and the lack of any requirement for any correlation between structure and function of the encoded Rig proteins.

Enablement

At pages 9 and 10 of the response Applicant argues that the specification is enabling because the scope of the term "Rig polypeptide" is clear, and because the specification teaches examples of how to use SEQ ID NO:5 or fragments thereof to detect or amplify a nucleic acid in a sample. Applicant relies for support on certain passages of the specification that describe the use of SEQ ID NO:5 or fragments thereof for these purposes. It is noted that the rejection states that the claims are enabled for the scope of using SEQ ID NO:5 or its fragments for these purposes. The specification fails to enable methods of using sequences other than SEQ ID NO: 5 or its fragments for these purposes. Applicant addresses this issue by stating that for nucleic acids encoding a Rig polypeptide other than the nucleic acid the nucleic acid having the sequence of SEQ ID NO:5, the steps of the claimed method would be the same as those that are enabled, except that the sequence of the probes might be different. Applicant asserts that one of ordinary skill in the art would know how to make any required changes primer design. This argument is unsupported. As noted above, the

breadth of the claims is unclear because it is unclear what is embraced by a "Rig polypeptide" or a "Rig nucleic acid" because it is unclear what are the minimal structural and functional requirements of these genuses. Further, the specification fails to provide any framework which can be used to accurately predict which amino acid substitutions will adequately maintain Rig structure and function. In view of these facts, the enabled scope of the claims is limited to methods of identifying and amplifying Rig nucleic acids using SEQ ID NO:4 or its complement, or fragments thereof.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 4 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Because the artificial chromosome comprises 105 kb of contiguous genomic sequence upstream of the start codon of the sequence encoding SEQ ID NO:5, it is clear that this nucleic acid comprises the transcriptional control elements for this open reading frame. For this reason, the bacterial artificial chromosome of Lamerdin is an expression vector for SEQ

ID NO:5. Because bacterial artificial chromosomes are replicated and maintained in bacteria, the disclosure of Lamerdin anticipates claim 4, requiring a prokaryotic host cell.

Thus Lamerdin anticipates the claims.

Claims 6-15 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al (Proc. Nat. Acad. Sci. USA 96: 214-219, 1999).

Yu teaches detection by Northern blot analysis of polyA RNA from human tumor tissue of a nucleic acid that encodes a polypeptide 63% identical to SEQ ID NO:5. See page 214, column 2, first full paragraph; paragraph bridging pages 215 and 216; and instant specification at page 43, lines 25-29 and page 4, lines 24-29. The probe was a set of random primed fragments of a NOEY2 cDNA. Yu also teaches identification of a Noey2 gene in genomic DNA *in situ* by hybridization with a nucleic acid containing Noey2. See Fig. 4 on page 217. As discussed above under 35 112, first paragraph rejections, Noey2 DNA has regions of complementarity to SEQ ID NO:4. Because Noey2 nucleic acids were identified probes with complementarity to at least part of SEQ ID NO:4, and because the specification does not exclude Noey2 from the genus of polypeptides that may be construed as Rig polypeptides, these methods of Yu anticipate claims 6-10.

The amplification methods of claims 11-15 require two oligonucleotides having complementarity to SEQ ID NO:4. However, the claims do not recite any minimum amount of complementarity required, so Rig amplification methods using

oligonucleotides having only a single base in common with SEQ ID NO:4 could anticipate the claims. Because SEQ ID NO:4 contains all four deoxynucleotide bases, any Rig amplification method using DNA primers could anticipate the claims. Yu teaches several methods of DNA oligonucleotide primer-mediated PCR amplification and detection of nucleic acids encoding Noey2. See e.g. first, second, fourth, and fifth full paragraphs of column 1 on page 215. Thus Yu anticipates these claims.

Response to Arguments

Applicant's arguments filed 7/31/03 have been fully considered but they are not persuasive.

Rejection over Lamerdin

Applicant argued at page 11 of the response that the bacterial artificial chromosome (BAC) of Lamerdin is not an expression vector, relying for support on Sambrook et al which teaches that BACs are used as high capacity vectors for replication of sequences. This argument is unpersuasive because the fact that BACs are used for replication does not mean that they cannot also be used as expression vectors. In fact, Baker, cited under 35 USC 103 rejections below teaches that BACs comprising eukaryotic chromosome fragments are used to study the function of eukaryotic promoters. See page 1950, column 1, lines 4-6 of Introduction. Clearly methods of studying promoter function entail methods of studying gene expression. Applicant did not argue that Lamerdin failed to teach a nucleic acid sequence encoding the polypeptide of SEQ ID NO:5.

Applicant argued that the rejection is overcome by limiting the claims to a recombinant expression vector consisting essentially of an open reading frame linked to one or more regulatory elements, wherein the open reading frame encodes a polypeptide set forth in SEQ ID NO:5. This amendment introduces into the claims the transitional phrase "consisting essentially of". MPEP 2111.03 states that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention, citing In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). Applicant has provided no evidence or argument that the BAC of Lamerdin materially affects the basic and novel characteristics of the claimed invention in any way, and the specification provides no indication of what is *essential* to the basic and novel characteristics of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355. If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also Ex parte Hoffman, 12 USPQ2d 1061, 1063-64 (Bd. Pat. App. & Inter. 1989). Applicant has not met this burden, and the rejection is maintained.

Rejection over Yu

Applicant argues that it is clear to one of ordinary skill in the art, in view of Figures 2 and 3, that the Noey2 polypeptide of Yu is not a Rig polypeptide. As discussed above under the response to arguments against the written description rejection, this argument is unpersuasive. Fig. 2 is simply an alignment of several Ras family members and does not provide any interpretation of the data that would support Applicant's position. Fig. 3 is a dendrogram depicting evolutionary relationships among Ras family members as a function of sequence divergence. This Figure does not support Applicant's argument because it presents no data concerning the relationship between structure and function, and therefore provides no evidence that any of the Ras proteins in the Figure would not be considered a Rig protein, particularly Noey2 which has in common with Rig 63% amino acid sequence identity and tumor suppressor function. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 2 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. The nucleotide sequence of Lamerdin differs from SEQ ID NO:4 by a single, silent base change in a glutamine codon at a position corresponding to position 70 of SEQ ID NO:5. The codon in SEQ ID NO:4 is CAA, whereas the codon reported by Lamerdin et al is CAG. Because CAA and CAG codons both encode glutamine, they are art-recognized equivalents. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence it would have been prima facie obvious to one of ordinary skill in the art to substitute the sequence of Lamerdin for that of SEQ ID NO:4.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 3 and 4 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999), in view of Kimmelman et al (Oncogene (1997) 15(22): 2675-2685), Der et al (US Patent 6,077,686, issued 6/20/2000), and Baker et al (Nucl. Acids. Res. (1997) 25(10): 1950-1956).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins.

Lamerdin does not teach a vector comprising a replication defective virus, or a eukaryotic host cell.

Kimmelman teaches the cloning of a RAS-related gene, its transfer to a plasmid expression vector, and analysis of expression of the encoded protein in eukaryotic cells. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

Der et al teach that expression vectors comprising plasmids or replication defective viruses are functional equivalents. See column 11, lines 58-67.

Baker teaches that transfection efficiency of bacterial artificial chromosomes to eukaryotic cells is inefficient. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to transfer the RAS-related open reading frame of Lamerdin to a plasmid or replication-defective virus. One would have been motivated to do so in order to facilitate analysis of the gene and its product because members of the Ras subfamily have been shown to be involved in signal transduction and tumorigenesis, and because determining the function of RAS-related genes is an important step in understanding the complexity of intracellular signaling. See e.g. Kimmelman abstract and page 2676, column 1, last paragraph prior to Results. One of ordinary skill in the art recognizes that transfer of the sequence from a 177 kb artificial chromosome to a different expression vector such as a plasmid or replication deficient virus would facilitate analysis of the gene, because higher transfection efficiency can be achieved with these vectors (see Baker above). MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious.

In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case Der teaches that plasmids and replication defective viruses may be used interchangeably as expression vectors, thus these are art-recognized equivalent components in the context of gene expression, and it would have been prima facie obvious to one of ordinary skill in the art to use either type of vector for the expression and analysis of the sequence of Lamerdin. On the other hand one could have improved the transfection efficiency of the baculovirus clone of Lamerdin by adding to it psoralen-inactivated adenovirus as taught by Baker. Because the adenovirus of Baker is inactivated, it is considered to be replication deficient, thereby meeting the limitations of claim 3.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 6-11, 13-15, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) in view of Kimmelman et al (Oncogene (1997) 15(22): 2675-2685).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins.

Lamerdin does not teach a method of detecting in a sample nucleic acids by Northern blot using a probe having complementarity to a portion of the nucleotide sequence of SEQ ID NO:4, or a method of amplifying nucleic acids by using PCR primers for amplifying SEQ ID NO:4.

Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and methods of detecting the corresponding mRNA

in a variety of human tissues by Northern blot of total cellular RNA. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681. It is noted that total cellular RNA comprises polyA RNA.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the Northern blot method of Kimmelman to detect nucleic acids encoding SEQ ID NO:5 in human tissues, including tumor tissues, using a probe comprising at least a portion of SEQ ID NO:4. One would have been motivated to do so because it is apparent from the teachings of Kimmelman that determining the pattern of expression of newly discovered RAS-related genes is essential to understanding their function, and because Kimmelman teaches that RAS-related genes are involved in tumorigenesis and are therefore of biomedical interest. See abstract, page 2676, column 1, last paragraph prior to Results, and paragraph bridging pages 2680 and 2681.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PCR amplification to transfer the sequence of Lamerdin from the bacterial artificial chromosome to an expression vector as taught by Kimmelman. See page 2682, column 2, lines 1-10 of paragraph bridging pages 2682 and 2683. One would have been motivated to do so because PCR allows one to insert restriction enzymes of choice onto the termini of a given open reading frame, as evidenced by Kimmelman who used PCR primers containing BamHI or EcoRI sites, thereby facilitating insertion into a vector of choice in an orientation of choice.

Thus the invention as a whole was *prima facie* obvious.

Claim 12 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and

Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 1, 6-11 and 13-15 above, and further in view of Mullis et al (US Patent 4,965,188, issued 10/23/90), and Takarada (US patent 5,981,183, issued 11/9/99).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not explicitly teach a DNA polymerase comprising both DNA- dependent DNA polymerase activity and RNA-dependent DNA polymerase activity.

Mullis teaches amplification of DNA sequences by polymerase chain reaction (PCR), using DNA polymerase from *Thermus aquaticus*. See *e.g.* claim 5.

Takarada teaches that DNA polymerase from *Thermus aquaticus* comprises both DNA dependent DNA polymerase activity and RNA dependent DNA polymerase activity. See column 9, lines 62-67.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the *Thermus aquaticus* DNA polymerase of Mullis to amplify the sequence of Lamerdin as taught by Kimmelman. One would have been motivated to do so because *Thermus aquaticus* DNA polymerase is stable at the high temperatures required for denaturation in PCR. See abstract of Mullis. The limitations of claim 12 are met because *Thermus aquaticus* DNA polymerase inherently comprises both DNA

dependent DNA polymerase activity and RNA dependent DNA polymerase activity. See Takarada.

Thus the invention as a whole was *prima facie* obvious.

Claim 15 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 1, 6-11 and 13-15 above, and further in view of Mullis et al (US Patent 4,965,188, issued 10/23/90).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not explicitly teach a method of amplifying RNA, as recited in claim 15.

Mullis teaches that PCR amplification of messenger RNA sequences allows an improvement in detection of target sequences without the use of radioactive labels. See column 7, lines 16-24 and paragraph bridging columns 19 and 20.

It would have been obvious to one of ordinary skill in the art at the time of the invention amplify mRNA sequences by PCR in order to characterize the pattern of tissues in which the sequence of Lamerdin was expressed, rather than Northern blotting

as taught by Kimmelman. One would have been motivated to do so because PCR allows greater sensitivity and would have obviated the need for the radioactive label use by Kimmelman.

Thus the invention as a whole was *prima facie* obvious.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 1, 6-11 13-15, and 29 above, and further in view of Erlich et al (US Patent 5,314,809, issued 5/24/94) and DeBoer et al (US Patent 5,397,703, issued 3/14/95).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

Erlich teaches that PCR primers may be modified by the inclusion of G and or C residues at their 5' ends in order to improve thermostability. See column 3, lines 35-42.

DeBoer teaches the modification of PCR primers to include both a 5' C-G clamp and a restriction site. See column 14, lines 9-11.

These references do not teach a oligonucleotides comprising SEQ ID NOS:2 and 3.

It would have been obvious to one of ordinary skill in the art at the time of the invention to synthesize for PCR oligonucleotide primers comprising SEQ ID NOS:2 and 3. One would have been motivated to do so in order to transfer the sequence of Lamerdin from a bacterial artificial chromosome to a plasmid expression vector having a higher transfection efficiency. In order to amplify and transfer the sequence of Lamerdin, one would have chosen primers corresponding to the 5' and 3' ends of the ORF of Lamerdin, as in SEQ ID NOS: 2 and 3. Additionally one would have been motivated to include restriction sites 5' to the portions of the primers corresponding to the ORF, in order to facilitate cloning of the resulting PCR fragment. For example, Kimmelman teaches the incorporation of Bam HI and Eco RI sites, as are incorporated into instant SEQ ID NOS: 2 and 3, respectively. See lines 1-10 of paragraph bridging pages 2682 and 2683 of Kimmelman. Finally, it is routine in the art to add G and or C residues to the 5' ends of primers in order to increase the thermostability of the primers. This is apparent from the teachings of both Erlich and DeBoer. In fact DeBoer teaches the combination of restriction sites and G/C clamps at the 5' prime ends of PCR primers.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 7/31/03 have been fully considered but they are not persuasive. At page 12 of the response Applicant asserts that the 103 rejections rely principally on GenBank Accession No. AC006538, and argues that this sequence does not comprise a recombinant expression vector consisting essentially of an open reading frame encoding SEQ ID NO:5 linked to one or more regulatory elements. This argument as it applies to the rejections of claims 1 and 2 over Lamerdin was addressed

above under *Rejection over Lamerdin*, and found to be unpersuasive for the reasons set forth above, i.e. because a BAC is a recombinant expression vector. Applicant did not address the issue of whether or not it would have been obvious to substitute a CAA codon for a CAG codon.

With respect to claims 1, 3, and 4, the Office showed that it was obvious to remove the open reading frame of Lamerdin from the BAC and transfer it to plasmid or viral expression vectors. Applicant's traversal of these rejections stated only that Lamerdin did not teach a recombinant expression vector. This is unpersuasive because Lamerdin was not relied upon in these rejections to teach an expression vector. Lamerdin was relied upon to teach a nucleic acid sequence encoding SEQ ID NO:5. Applicant did not argue that there would be no motivation to remove the ORF of Lamerdin from the BAC and transfer it to the cited recombinant expression vectors.

With regard to claims 6-16, and 29, Applicant's arguments that Lamerdin fails to teach a recombinant expression vector are misplaced because these claims do not require a recombinant expression vector. In any case Lamerdin was not relied upon in these rejections to teach such. Lamerdin was relied upon to teach a nucleic acid encoding SEQ ID NO:5 which could b used as a probe, or could be amplified by PCR. Applicant presented no evidence or argument that the nucleic acid of Lamerdin did not encode SEQ ID NO:5, that there would be no motivation to use the nucleic acid as a probe to detect target nucleic acids, or that these target nucleic acids would not encode some species of Rig. Similarly Applicant presented no evidence or argument that one

would not have been motivated to amplify the nucleic acid of Lamerdin as discussed in the rejections.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.